commodations were tightly closed, while beneath was a cargo of ferro-silicon. The deaths were at first supposed to be from cholera, or possibly from ptomain poisoning, but these causes were subsequently excluded. The only noticeable symptoms found on post-mortem examination were connected with the lungs, which were in all cases strongly congested with dark venous blood. Cultures from the stomachs and intestines showed in several instances the presence of numerous vibrios, which so closely simulated those of cholera that they were with great difficulty distinguished from these. Suspicion was finally turned to the ferro-silicon as the cause of death and a series of experiments instituted which revealed the fact that under the influence of moisture poisonous gases are given off. Mice placed in jars over ferro-silicon soon showed symptoms of dulness and somnolency. When the ferro-silicon was moist, death preceded by disturbances of movement ensued in a few hours. Guinea-pigs under similar conditions succumbed in ten hours. The only abnormal feature on post-mortem examination was congestion of the lungs, such as is usually seen in cases of suffocation. Experiments were further instituted to determine what gases were responsible for the fatal results. Acetylene and hydrogen silicid were excluded and arsin found only in traces. Small quantities of phosphin (phosphoretted hydrogen) were found to be present, and this seems to be the principal poisonous constituent of the emanation. While little is known of the toxicology of phosphin, it is stated to be so poisonous that 0.02 per cent. of it in the air is fatal to small animals in half an hour. As ferro-silicon is formed by heating iron ore, quartz, coke and lime in an electric furnace, and as phosphorus is usually present in at least two of these constituents, phosphids, which evolve phosphin on treatment with water, would be present in ferro-silicon.

This investigation has served to throw light on several deaths which have been recorded in the past three years, which were undoubtedly due to ferro-silicon. In August, 1907, four persons died on the steamer *Olaf Wijk*, which was carrying ferro-silicon as part of its cargo. A short time before two children are recorded as dying on a Rhine steamer, having slept in a close cabin immediately over ferro-silicon, which composed a part of the cargo of the vessel. Four other cases of death on vessels carrying ferro-silicon are recorded, where the cause of death was not at the time suspected, but which are probably to be attributed to ferro-silicon.

As ferro-silicon is now used on a large scale in steel making, it is desirable that attention should be called to the fact that certain precautions should be taken in its transportation, especially that it shall be kept as dry as possible, and that it shall be well ventilated.

J. L. H.

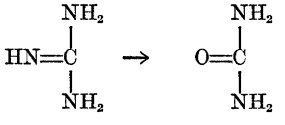
## *SPECIAL ARTICLES*

### THE PHYSIOLOGICAL SIGNIFICANCE OF CREATIN AND CREATININ[1]

Two fundamental observations have furnished the incentive to investigation and given the direction to hypotheses on the topic under discussion to-day. One of these was the discovery of *creatin* as a constant constituent of the muscular tissues of vertebrates; the other was the presence of *creatinin* in the urine of the higher animals. Creatin can be changed by the action of acids into creatinin, which in turn is supposed to form creatin in alkaline solutions. Since the chemist is able so readily to convert each of these compounds into the other in the laboratory, it was quite logical for the physiologist to assume some genetic relation between them in the living body. Creatin was looked upon as a product of protein metabolism in muscle, easily converted into its "anhydride" creatinin and thus eliminated in the urine. From this point of view two possible sources of urinary creatinin early suggested themselves, namely, an *exogenous* source in the muscle tissue (meat) consumed as food; and an *endogenous* origin,

[1] Papers read at the joint session of Section K —Physiology and Experimental Medicine—of the American Association for the Advancement of Science and the bacteriologists, biochemists and physiologists, Baltimore, December, 1908.

in the living muscles of the body itself. It was a further short step to associate muscular contraction with alterations in the creatin content of the contractile tissues; and to look for variations in creatinin output in relation to the muscular work done by the individual. In addition to this the creatin of the muscles has, because of its structural relationship, been discussed in the past as an important precursor of urea, on the assumption that the guanidin rest can be readily converted to urea in metabolism:



Ten years ago Dr. F. G. Hopkins wrote:

> The *variations* in the urinary creatinin generally follow very closely those of urea, but there can be no doubt that its quantity depends largely on the amount of creatin taken with the food.

At that time the story was as simple as it was brief. The creatin of the muscle was in some way derived from the proteins of the body; the creatinin of the urine was referable to the creatin ingested or furnished by the muscles of the body. Feeding experiments with meat and its products seemed to bear out this view and analogies lent further support.

From the outset the study of these problems was hampered by the lack of a suitable process for the estimation of these compounds. The Neubauer method, in which creatinin is isolated as a double salt with zinc chloride, was practically the only one available. Older testimony and more recent critical investigations leave no doubt that this method is utterly unreliable as a quantitative procedure for the estimation of creatinin. All of the earlier work based upon it must therefore be attended with a probability of error which has necessitated a revision of the entire subject. Here, as in so many other instances in scientific research, a good experimental method has opened up entirely new fields of observation; and to Professor Folin is due the credit for a satisfactory quantitative procedure for estimating creatin and creatinin based on Jaffé's color test with picric acid and an alkali. It has given the impetus to numerous investigations since its publication in 1904; in truth, this method, the simplicity of which makes it available in every clinic, has been responsible for a revolution in some of our ideas of metabolism. I propose to present some of these newer aspects of the physiology of creatin and creatinin, and to view them in the light of recent investigation; to inquire to what extent certain current hypotheses are justified. Bear in mind that a brief review within the limits of a symposium can neither be exhaustive nor do full justice to the newly accumulated mass of evidence; it is intended to be suggestive rather than critical—to propound problems rather than solve them.

Let us first consider the significance of creatin and creatinin in the muscle. The evidence now seems conclusive that creatinin is not present preformed in the muscular tissues (Grindley and Woods; Mellanby, '08; Mendel and Leavenworth). The fact that chemical manipulations of the extracts of muscle are quite likely to convert creatin into creatinin explains the constant occurrence of both of these compounds in commercial extracts of meat; and it warns against all conclusions regarding the physiological conversion of one compound into the other whenever appropriate conditions of analysis have not been rigorously maintained. When it is remembered that mere evaporation on a water-bath, under the acid reaction which arises post mortem, is sufficient to induce the conversion of creatin into creatinin, the liability of analytical error is emphasized. The difficulties are further increased by the fact that *quantitative* conversion of creatin into creatinin for analytical purposes is likewise attended with undeniable uncertainty (Folin, '06). These features are mentioned at the outset because they have served to complicate the experimental results to a degree where nothing short of experience seems to furnish adequate critique of the claims of investigators.

Creatin has been found in the muscles of all vertebrates which have been examined for it. From the phylogenetic point of view it is interesting, on the other hand, to note the absence of creatin from invertebrate muscle.

As we descend the scale it is still found in the lamprey, but missing in the arthropoda—the lobster and horseshoe crab, for example (Mellanby, '08; Lyman). This is only one of the chemical differences between vertebrate and invertebrate muscle and at once raises the question whether it is at all likely that creatin is functionally associated with contraction of muscle. Creatin apparently occurs in the non-striated variety of vertebrate muscle which is so frequently (and I believe without experimental justification) compared directly with the muscles of invertebrates (Saiki). Unfortunately, most of our information is still based upon the outcome of color tests rather than actual isolation experiments. Generally speaking the quantity of creatin seems to be larger in the muscles of warm-blooded animals, the hedgehog furnishing an unexplained exception in this series (Mellanby, '08).

Creatin is present in the embryonic tissues in mammals and in the developing chick, in which latter case it must be directly synthesized from the food-supply. Creatinin has not been found at any time (Mendel and Leavenworth; Mellanby, '08). In the chick the formation of creatin is apparently synchronous with, but independent of, the growth of the muscle. Mellanby has attempted to correlate the rapid increase in creatin during the later embryonic period with correspondingly rapid development of some organ, and naturally refers to the liver. He argues that since the cross-striated muscles of the invertebrates are identical with those of vertebrates —a contention which we are not inclined to admit as conclusive—and are creatin-free, muscle can not account for the phylogeny of creatin. Mellanby adds as a further biological speculation that since the "gland of the mid-gut" of invertebrates has no morphological or physiological connection with the liver of vertebrates, this newly introduced organ might account for the origin of creatin in vertebrate metabolism.

How constant is the creatin content of adult muscles; and is it altered during activity? In the light of the meager and conflicting data available to-day, a satisfactory answer can not be given to these questions. Yet they are of fundamental importance for any adequate discussion of the rôle of creatin. Mellanby's convincing experiments on isolated muscles showed that muscular work leaves creatin unaffected, as does the survival of muscle. The stability of muscle creatin is the keynote of his contentions. On the other hand, Graham-Brown and Cathcart reported an increase in the so-called total creatinin in stimulated frogs' legs when the organs were isolated, and a decrease when the circulation remained intact. Weber and Howell and Duke have observed that the vigorously beating isolated heart gives more of these compounds to the fluid perfusing it, than does the quiescent organ. In this connection it is of interest that, according to Ujano, the creatin of the muscle appears to be held in some non-diffusible form in the contractile tissue and is only released when the integrity of the muscle bundles is impaired. This observation may help to explain the unique property of muscle tissue to contain such conspicuous quantities of the compound.

We must bear in mind that all experiments such as those just reported are conducted under artificial conditions different from what pertains in normal muscular activity. The isolated or perfused muscles are working both without adequate repair of the contractile substance and under impoverished nutritive conditions. A disintegration of the tissues with possible liberation of creatin under such circumstances may be an incident in this *abnormal* situation rather than a customary expression of muscular contraction; just as we know that certain features of metabolism in starvation are the evidence of extraordinary katabolic changes rather than normal sequences. At any rate, we need to know more about the actual creatin content of muscle under a variety of both normal and unusual conditions, such as rest, activity, starvation and muscular disease, before the final word can be spoken.

The study of the metabolism of creatin and creatinin has lately received a new trend through the work of Gottlieb and his collaborators (Gottlieb, Stangassinger, Rothmann). An elaborate investigation of the behavior of

these compounds in autolysis led him to postulate that they can undergo a series of enzymatic transformations in the body, as follows: (1) Creatin can be formed in the autolysis of muscles and other organs. (2) Preformed or added creatin can be converted by enzymatic means into creatinin during autolysis. (3) In the progress of autolysis both of the compounds are destroyed by appropriate enzymes, creatase and creatinase. (4) The interaction of these processes affords a complicated curve for the creatin- and creatinin-content of autolyzing tissue extracts, since formation, conversion, and destruction may simultaneously go on. The behavior of creatin in the autolysis of different organs will vary according to the preponderance of one or the other of these different fermentative activities.

When we take into account the variations in the occurrence of these intracellular enzymes in the different tissues and note that the actual amount of creatin or creatinin found in an experiment at any moment represents the equilibrium point for a number of interdependent reactions the complexity of the situations becomes apparent. Truly a "bewildering array" of enzymatic processes, as Mellanby intimates in his severe critique of Gottlieb's work. Mellanby attributes the disappearance of creatin and creatinin to contaminating bacterial influences in these experiments; and he characterizes the conversion experiments as unconvincing because of the inappropriate analytical manipulations. Mellanby himself reports uniformly negative results on the behavior of creatin in autolysis. The repetition of these researches on the autolysis of tissues under more satisfactory conditions of control has, however, induced a number of investigators (van Hoogenhuyze and Verploegh, '08; Rothmann; Lefmann) to maintain the essential importance of endoenzymes in the metabolism of the compounds under discussion. Dakin has shown that arginase will not act upon creatin. The theory of the enzymatic transformation of creatin is comparable in many respects with accepted ideas regarding the metabolism of purins and other cellular products, and furnishes an attractive working hypothesis; it must, however, be admitted with reserve, if at all, until it rests upon a more substantial basis than the uncertain evidence of a color reaction.

This brings us to the facts in regard to the elimination of creatin and creatinin. The normal urine of healthy individuals contains no creatin whatever, or at most only traces. Folin's well-known observations demonstrated that the output of creatinin in an individual is practically constant despite very wide ranges of (creatinin-free) diet. This fact, now abundantly verified in many laboratories, led to the conclusion that the excreted endogenous creatinin is the expression of the true tissue katabolism, as distinguished from the exogenous protein katabolism consisting of a series of rapid hydrolytic cleavages resulting in the elimination of protein-nitrogen as urea. As might be expected, the output varies with the bulk of the metabolic tissues of the body, averaging about 15 to 20 milligrams per kilogram of body weight. The attempt to connect the excreted creatinin with tissue creatin has brought to light an apparent independence of these compounds in metabolism. Ingestion of creatinin results in increased creatinin elimination; but when creatin is fed to man or animals the creatinin content of the urine is scarcely altered, if at all (Folin, '06; Klercker; van Hoogenhuyze and Verploegh; Lefmann). Observations by Lefmann also uphold this for creatin introduced parenterally. It would appear, then, that creatin, when fed, is not converted to any extent into creatinin in the body. Furthermore, in distinction from creatinin, the creatin of the diet reappears at best only in small part as such in the urine. In the noteworthy feeding experiments of Folin the nitrogen of the creatin which disappeared was in some cases assumed not to be recovered in any form in the urine, especially where the diet was deficient in protein. Folin has advanced the tentative hypothesis that creatin may be one of those special products which serve to maintain the nitrogen equilibrium in the living tissues, but which do not easily take part in the urea-forming process; hence the muscle is found rich in creatin. When the organism is daily supplied with an abun-

dance of protein it may be preparing as much creatin as is needed for the maintenance of its normal supply. Creatin given with the food is consequently not retained by the muscles to the same extent as when the food contains an insufficient supply of protein.

Widely quoted as these experiments have been, they are scarcely conclusive on this point. Van Hoogenhuyze and Verploegh ('08) have lately maintained that the variations in the daily nitrogen output are large enough to exceed the quantities which Folin failed to recover when creatin was fed with a low diet. All feeding experiments are further complicated by the difficulty of ascertaining whether creatin is to any considerable extent destroyed by bacteria in the alimentary tract and thus escapes absorption as such. At present there is no way of telling what became of the creatin-N in the feeding experiments on record.

If, as we have learned, ingested creatin fails to increase appreciably the output of creatinin in the urine, must we not admit that the creatinin of the urine has an origin quite independent of the creatin of the muscle? "It would be most remarkable," writes Klercker, "if the endogenous creatin of the muscle were changed into creatinin in the body, whereas ingested creatin is not transformed in this way." It is, however, no more remarkable than the fact that ingested cystin may be completely oxidized in patients who are at the same time excreting the cystin which arises in their intermediary protein metabolism.

The recent investigations with the Folin method have shown that neither increased nor decreased muscular activity uncomplicated by other factors has any effect upon the excretion of creatinin (van Hoogenhuyze and Verploegh, '05; Shaffer, '08). This fact of itself can not speak against the origin of creatinin from creatin so long as it is not known what part creatin may play in the contraction of muscles. Shaffer has calculated a "creatinin-coefficient," representing the milligrams of excreted creatinin-N per kilogram of body weight, in a large number of individuals. This "coefficient" is regularly found low in individuals with lowered muscular efficiency and shows a parallelism with the muscular development and strength. He concludes that creatinin is not an index of the total endogenous protein katabolism, but is probably derived from, and an index of, some special process of the normal metabolism taking place largely, if not wholly, in the muscles. And upon the intensity of the process appears to depend the muscular efficiency of the individual. As a theory of metabolism this statement affords us little help; but as an expression of fact it elucidates a variety of interesting conditions. Thus the coefficient is found low in women, who as a rule are less developed muscularly than men; in infants with small bulk of muscular tissue; in the feeble aged; and in patients convalescent from wasting disease.

Creatin, not present in normal urines unless creatin is taken as food, is found in the urine during inanition and in certain pathological states. In starvation the creatinin output has been found to diminish gradually with the progress of the inanition. This is true likewise of another endogenous product, uric acid. The unique appearance of creatin under these circumstances must be borne in mind wherever this substance is found accompanying abnormal conditions attended by inadequate nutrition. In every such case it is reasonable to ascribe the source to the creatin of the muscles. Creatin may be excreted in acute fevers and various manifestations where there is a rapid loss of muscle proteins. Large outputs have been found in the urine of women during the first week post partum, when resolution of the uterus is taking place (Murlin; Shaffer). The fact that the creatinin elimination bears no appreciable relation to creatin in these conditions speaks further for the biological independence of the compounds.

There are numerous data already on record in attempts to connect the liver and other organs with the phases of metabolism which we are considering. It is almost too early to interpret these adequately because of the complexity of factors involved (Mellanby, '07; Spriggs, '07; van Hoogenhuyze and Verploegh, '08). In many instances, especially in the cases of hepatic disease, under-nutrition is an ever-present complication. Other cases, such as the muscular dystrophies with lowered cre-

atinin output, have a more immediate interest. Clinical investigators seem to forget that in these experiments of nature one rarely deals with simple conditions where a single organ, such as liver or muscle, is independently involved.

To attempt to formulate a theory of creatin and creatinin metabolism at this time would, in my judgment, be premature. It may, however, help us to crystallize the discussion by outlining some salient points of view. I think it will be agreed that the muscle plays a comparatively small part in the formation of creatinin. Let us assume for the moment that creatin represents a metabolism product originating in various organs, perhaps notably in the liver. It is transported about and especially deposited in the muscle in some non-diffusible combination. Most of it will be destroyed in ways that may be facilitated by enzymes. Here again it appears likely that the liver plays a prominent rôle. A part may be changed to creatinin, which may in turn be either destroyed or excreted. For this part of our hypothesis the evidence is most uncertain. Creatinin behaves as a waste product; it is decomposed with greater difficulty than is creatin, and it is eliminated more readily. But whether it represents a real end product, or like uric acid is an intermediary product, the output of which we associate with a balance between productive and destructive processes, can not yet be determined. At any rate, unchanged creatinin is promptly excreted and is nowhere to be found in detectable quantities in the organism. When the functional activities of the body are depressed or stimulated corresponding variations in creatin production and destruction may go on (van Hoogenhuyze and Verploegh, '08). So long as effective katabolic powers are maintained, the variations in creatinin output will be slight at most and in correspondence with the physiological state. Any excess of creatinin will represent only a fraction of the undestroyed increase in creatin. From this point of view the muscles would furnish creatin only as physiologically active organs and not as an incident of their contraction. The energy for contraction comes from quite different sources. When, however, the tissues are drawn upon for supplies, as in hunger or cachexia, creatin is liberated by the disintegrating muscle; and owing to the lowered effectiveness of the katabolic organ, let us say the liver, the creatin now escapes destruction and is eliminated as such. In other words, in normal metabolism creatin is continually produced and destroyed, or converted to creatinin which is speedily eliminated. In starvation preformed creatin is liberated; and neglecting to experience the customary destruction, it escapes unchanged. Here creatin is a product both of metabolism and of tissue resolution.

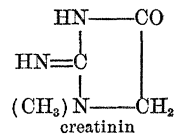
It is an easy task to offer objections to the outline just presented. A primary source of difficulty lies in the failure of most investigators to demonstrate that creatin, introduced into the circulation, in any way affects the output of creatinin. I have already spoken of this fact. Perhaps we have not yet succeeded in imitating the conditions of equilibrium which pertain in normal metabolism. Mellanby has protested against the conventional interpretation and lays primary emphasis upon creatinin, which he regards as being continually formed in the liver from substances brought to it. In the developing muscle this is changed to creatin and stored as such until a saturation point is reached, whereupon creatinin is continuously excreted. Mellanby urges that from a chemical point of view it is easier to assume the preliminary production of a cyclic structure like creatinin and its subsequent conversion to creatin, than the reverse process. Creatin is neutral and innocuous, and not likely to be changed to the strongly basic creatinin. The argument is teleological and not convincing; and to the liver are ascribed functions for which there is little evidence under either theory.

More profitable than this hypothetical discussion will be a consideration of some of the investigations which are immediately demanded. At the outset we need to know more definitely about the possible distribution of creatin in the tissues and blood; and above all, whether the creatin content of the muscle is normally a constant, as some maintain, or subjected to variations incident to activity,

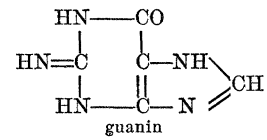
growth or atrophic changes. In view of the growing mass of data on the fate of ingested creatin and creatinin there is an unfortunate paucity of information regarding the changes which they experience after parenteral introduction into the body, where the uncertainties of change or loss in the alimentary tract are obviated and exact dosage becomes a possibility. The tendency to relegate important metabolic functions to the liver points to the desirability of studies on the fate of the nitrogenous katabolites in animals in which the hepatic functions have been excluded. In the only reference which I have found on this point, creatin was reported in noteworthy amounts in the urine of a dog after the Eck fistula operation and further extirpation of the liver (Salaskin and Zaleski).

The questions raised by the discussions regarding the intervention of enzymatic processes are timely and preeminently significant. Here, however, the limitations of the present colorimetric method are most likely to impede satisfactory progress and they invite the consideration of the analyst. The nature of the relation between inanition and excretion of creatin must be analyzed into its possibilities. Are we dealing with a general depression of katabolic organs in inanition? Or is the absence of metabolizable energy-yielding products in the tissues the sole factor? These questions are being investigated at present in our own laboratory. The behavior of the creatin bodies in the presence of microorganisms of the alimentary tract likewise deserves study, especially in view of the constant finding of methylguanidin among the products of bacterial action on creatin (Nawiasky), and of methylguanidin and dimethylguanidin in the urine (Achelis).

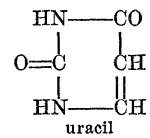
One can not conclude this topic without reference to the possible nitrogenous precursors of creatin and creatinin in the body. Speculation has been rife and claims have been numerous. That protein feeding does not *per se* increase the output in the urine has been conclusively demonstrated. Experiments with nucleic acid compounds (with thymus glands) which yield purin and pyrimidin derivatives structurally similar to creatinin, have had a negative outcome (Burian; Jaffé; Dorner; Lefmann).



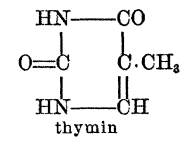
creatinin



guanin

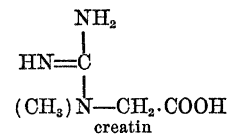


uracil

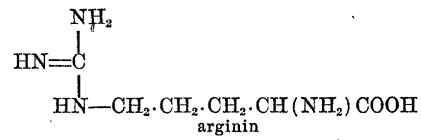


thymin

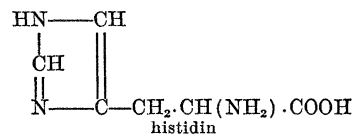
The experience with methylguanidin and with glycocyamin (guanidin acetic acid) is negative or uncertain at best (Jaffé; Dorner; Achelis). W. Koch's hypothesis relating creatinin to the metabolic change of methyl groups in the body and connecting it with the metabolism of the phosphatids (lecithin and kephalin) remains an interesting but unverified assumption. The guanidin derivate arginin stands structurally in close relation to creatin; while histidin, with its imidazole structure presents little more than analogy.



creatin



arginin



histidin

With neither of these compounds have experimental relations to creatin and creatinin been established. The nature of their synthesis still remains within the realms of surmise, inviting the organic chemist, as has so often been the case in biology, to supplement the efforts of the physiologist.

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## *THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE*

### *SECTION D—MECHANICAL SCIENCE AND ENGINEERING*

THE meetings of the section were held in the lecture rooms on the third floor of the chemical laboratory of the Johns Hopkins University. In the absence of President G. F. Swain, the vice-president of Section D, Professor Mansfield Merriman, was chosen to preside over the meetings of the section.

Professor C. A. Waldo was elected a member of the council.